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13. Abstract ***(Maximum 200 Words)*** (abstract should contain no proprietary or confidential information)

The underlying hypothesis of our study is that quantitative breast elasticity imaging is possible and provides unique information, which could increase the detection, characterization and monitoring of potentially malignant masses in the breast. The purpose of this study is to develop a new modality of medical imaging for surrogate palpation of deep lying breast lesions, namely Acousto-Mechanical Imaging, or AMI, capable of producing high-resolution images of elastic (Young's or shear) moduli. In our method, the evaluation of mechanical structure and properties of an object is accomplished via the synergy of the surface stress pattern measured by the force sensor array and the internal strain obtained by an ultrasound imager. Acousto-mechanical imaging, therefore, consists of three main components: evaluation of externally induced surface pressure and internal tissue motion; estimation of strain and stress tensor components; and reconstruction of the spatial distribution of the elastic modulus using displacement, strain and stress images. An ambitious research plan has been developed to address important engineering and clinical aspects of AMI. The overall program is designed to critically test the hypothesis that AMI can non-invasively detect and monitor breast lesions thus providing a valuable clinical tool for breast cancer diagnosis, monitoring and therapy.

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INTRODUCTION:

The underlying hypothesis of our study is that remote, non-invasive measurements of breast elasticity are possible and provide unique examiner-independent information, which could increase the detection, characterization and monitoring of potentially malignant masses in the breast. The purpose of this study is to develop a new modality of medical imaging for surrogate palpation of deep lying breast lesions, namely Acousto-Mechanical Imaging, or AMI, capable of producing high-resolution images of elastic (Young's or shear) modulus. In Acousto-Mechanical Imaging, the evaluation of mechanical structure and properties of an object is accomplished via the synergy of the surface stress pattern measured by the force sensor array and the internal strain obtained by the ultrasound imager. Acousto-mechanical imaging, therefore, consists of three main components: evaluation of externally induced surface pressure and internal tissue motion; estimation of strain and stress tensor components; and reconstruction of the spatial distribution of the elastic modulus using displacement, strain and stress images. An ambitious research plan has been developed to address important engineering and clinical aspects of Acousto-Mechnaicl Imaging. The overall program is designed to critically test the hypothesis that Acousto-Mechanical Imaging can non-invasively detect and monitor breast lesions thus providing a valuable clinical tool for breast cancer diagnosis, monitoring and therapy.

BODY:

One of the arising areas of ultrasonic medical diagnostics is Elasticity Imaging (EI) [Cespedes et al. 1993, Sarvazyan et al. 1998, Emelianov etr al. 1995, Chenevert et al. 1998]. Recently, an alternative method of imaging tissue structures in terms of their elasticity, the method of Mechanical Imaging (MI), has emerged [Sarvazyan 1998 and 1999]. The underlying hypothesis of these approaches is that remote, non-invasive measurements of elasticity in the breast are possible and provide unique examiner-independent information, which could increase the detection, characterization and monitoring of potentially malignant masses in the breast. The purpose of this study is to develop a new modality of medical imaging for surrogate palpation of deep lying breast lesions, namely Acousto-Mechanical Imaging (AMI), capable of producing high-resolution images of elastic (Young's or shear) modulus. AMI includes unique features of both EI and MI, where the data on the stress pattern measured by the force sensor array of MI complement the strain data obtained by ultrasonic EI device. Synergy of these two complementary methods results in superior diagnostic potential of AMI compared to EI and MI separately. Also, for breast imaging, AMI will be used as an important and valuable adjunct to existing ultrasound imaging and mammography.

Changes in soft tissue elasticity are usually related to pathological processes. The success of palpation as a diagnostic tool is evidence of this. Even today, palpation is widely used as a self-screening procedure for hard masses in the breast. Its efficacy, however, is limited to abnormalities located relatively close to the skin surface, and the information obtained is inherently subjective. Nevertheless, differences in elasticity (Young's or shear

moduli) between normal and pathologically changed breast tissue can be several orders of magnitude [Sarvazyan 1998]. Because of this, there has been consistent scientific and clinical interest in tissue elasticity.

The evaluation of mechanical structure and properties of an object requires knowledge of the spatial distribution of both stress and strain. The main objective of the work described in this proposal is to utilize strain and stress data measured simultaneously and, consequently, to remotely evaluate the mechanical properties of an investigated tissue with minimal ambiguity. Indeed, ultrasound-based elasticity imaging derives information on tissue elasticity from directly evaluated strain data and using various indirect [Cespedes et al. 1993] or reconstructive [Emelianov et al 1995] methods to estimate necessary stress data. The stress in a real three-dimensional system with localized inclusions is of a complex character, and it is difficult to estimate the stress pattern without direct measurements. Various theoretical assumptions for stress pattern evaluation used in ultrasonic elasticity imaging are not accurate or rigorous and do not provide an adequate description of the mechanical state of the system.

The AMI method is free from this shortcoming. The paramount element of an AMI device is a force-sensing array incorporated on the ultrasonic probe surface contacting the tissue. This combined ultrasonic and pressure array probe is, therefore, capable of simultaneous registration of surface stress and internal strain patterns in tissue necessary for subsequent unambiguous and artifact free elasticity imaging. Acousto-mechanical imaging (AMI) consists of three main components: 1) evaluation of externally induced surface pressure and internal tissue motion using the AMI probe as described above; 2) estimation of strain and stress tensor components; and, finally, 3) reconstruction of the spatial distribution of the elastic modulus using displacement, strain and stress images.

An ambitious research plan has been developed to address important engineering and clinical aspects of AMI development. A very competitive group of researchers with extensive experience in elasticity imaging (Biomedical Engineering Department, University of Michigan, Ann Arbor, MI), mechanical imaging (Artann Laboratories, East Brunswick, NJ) and clinical radiology and pathology (University of Michigan Medical School, Ann Arbor, MI) with emphasis on breast diagnosis was formed for this project. The overall program was designed to critically test the hypothesis that acousto-mechanical imaging can non-invasively detect and monitor breast lesions, thus providing a valuable clinical tool for breast cancer diagnosis, monitoring and therapy. The proposed program included fundamental studies of merging elasticity and mechanical imaging methods. In particular, a pressure-sensing array compatible with ultrasound scanhead operation was designed, and signal processing algorithms for stress and strain estimation was developed. In parallel with these tasks, several phantoms mimicking normal breast and breast with several pathologies were fabricated to test developed hardware and software. Finally, a prototype of the AMI system appropriate for clinical breast elasticity imaging studies was designed, built and tested.

The results presented here represent the product of twelve months of work. In the remainder of this section we present detailed results from each of the proposed areas. Please note that no human subjects were part of the original proposal.

Design of pressure sensing array:

The design and development of the pressure-sensing array is of paramount importance for acousto-mechanical imaging. The pressure-sensing array must be compatible with ultrasound scanner and maintain high resolution and sensitivity while each element remains miniature to allow high-resolution surface stress imaging. After a period of trial and error, we have finally identified Pressure Profile Systems, Inc. (Los Angeles, CA) as the potential supplier of the sensor pad. The Pressure Profile Systems has actively worked with researchers at both the University of Michigan and Artann Laboratories, Inc. (East Brunswick, NJ) to design and fabricate the desired pressure-sensing array. One of such arrays, fully interfaced with ultrasound transducer is presented in Fig. 3 and further discussed below.

Stress and Strain Imaging:

The goal of elasticity reconstruction in acousto-mechanical imaging is to estimate an unknown distribution of Young's modulus based on the simultaneous and synchronized measurement of normal stress at the surface $S_{\sigma u}$ and internal displacement within the ultrasound imaging plane S_I (Fig.1).

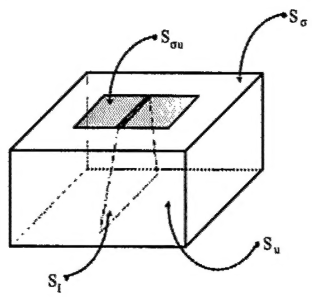


Figure 1: Schematic representation of acousto-mechanical imaging setup. The deformations are applied at the $S_{\sigma u}$ surface where the normal stress pattern is measured while internal displacements are measured within the ultrasound imaging plane S_I.

Determining the elastic modulus in inhomogeneous material from responses to a fixed mechanical action is possible by using a number of formulations [Skovoroda et al 1995 and 1999a]. For example, in ultrasound elasticity imaging, if all necessary components of the internal strain are measured, then reconstruction algorithms based on the mechanical equilibrium equations can be used to describe the unknown distribution of relative elasticity without additional assumptions. However, if any assumptions about the object can be made, then a more robust model-based reconstruction can be performed [Emelianov et al 1998]. Indeed, most of the breast lesions can be modeled as rounded inclusions. Therefore, the model of an elastic sphere in a heterogeneous background can be used. Since this elasticity imaging approach assumes a straightforward model such as this, reconstruction in the vicinity of the lesion is far less susceptible to noise. We have already developed [Skovoroda et al 1994; Sarvazyan and Skovoroda 1996; Skovoroda and Sarvazyan 1999] and successfully applied the model-based reconstruction approach to study elasticity imaging [Emelianov et al 1998]. This model is based on general theory of elasticity for incompressible medium. Indeed, most soft tissues are incompressible materials with Poisson's ratio approaches 0.5 [Sarvazyan et al 1995].

In general, the statically deformed inhomogeneous elastic medium must satisfy the well-known equilibrium condition

$$\sum_{j=1}^{3}\frac{\partial\sigma_{ij}}{\partial x_j}=0 \qquad i=1,2,3 \ ,$$

where σ_{ij} is one component of the 2nd ranked stress tensor, u_i is the displacement in the x_i direction of the Cartesian system of coordinates. This equation must be satisfied at every internal point of the body.

Assuming linear elasticity and accounting for tissue incompressibility, the components of the stress tensor in an isotropic, continuous incompressible medium are:

$$\sigma_{ij} = p\delta_{ij} + 2\mu\varepsilon_{ij} \ ,$$

where p is the static internal pressure, δ_{ij} is the Kronecker delta symbol, μ is the shear elastic modulus, and ε_{ij} is one component of the 2nd ranked symmetric strain tensor, defined as

$$\varepsilon_{ij}=\frac{1}{2}\left(\frac{\partial u_i}{\partial x_j}+\frac{\partial u_j}{\partial x_i}\right) \ .$$

In addition, for incompressible materials such as soft tissues, the shear and Young's (E) modulus are simply proportional, $E=3\mu$. That is, for static deformation, an incompressible mechanical body will act solely as an elastic body, completely characterized by either shear (μ) or Young's (E) modulus. Therefore, the goal of elasticity reconstruction is to evaluate the spatial distribution of either elastic moduli. Within this application, reconstruction of Young's modulus E will be explicitly addressed.

The proposed model is a generalization of the solution [Goodier 1933] of stress and strain distribution around spherical inclusion. In the developed model, the solution of equilibrium equation is

$$u_r=\frac{1}{4}U(r)[1+3\cos(2\theta)]$$

$$u_\theta=V(r)\sin(2\theta)$$

$$u_\varphi=0$$

$$p=P_0(r)+P_1(r)[1+3\cos(2\theta)] \ ,$$

where the center of the spherical (r, θ, φ) system of coordinates is placed at the center of a lesion such that the direction $\theta=0$ is parallel to the direction of an applied deformation. Using the incompressibility condition and substituting displacements and pressure into equations of equilibrium, we find that

$$V=-\frac{1}{4}\left(r\frac{\partial U}{\partial r}+2U\right)$$

$$P_1=-\frac{1}{72}\left[\frac{\partial E}{\partial r}\left(r^2\frac{\partial^2 U}{\partial r^2}+2r\frac{\partial U}{\partial r}+4U\right)+E\left(r^2\frac{\partial^3 U}{\partial r^3}+6r\frac{\partial^2 U}{\partial r^2}\right)\right], \quad P_0=\text{constant} \ ,$$

and $U(r)$ is, therefore, coupled with unknown Young's modulus $E(r)$:

$$r^4\frac{\partial^4 U}{\partial r^4}+a_3r^3\frac{\partial^3 U}{\partial r^3}+a_2r^2\frac{\partial^2 U}{\partial r^2}+a_1r\frac{\partial U}{\partial r}+a_0U=0 \ ,$$

with

$$a_3 = 2\,(4+\gamma r),\ \ a_2 = r\,(r\,\Gamma + 10\gamma),\ \ a_1 = 2\,(r^2\,\Gamma - 3\gamma r - 12),$$

$$a_0 = 4\,(r^2\,\Gamma + 6)\,,\ \gamma = \frac{1}{E}\frac{\partial E}{\partial r}\,,\ \Gamma = \frac{1}{E}\frac{\partial^2 E}{\partial r^2}\ .$$

Note that the variations of Young's modulus are incorporated in the coefficients a_i of this differential equation. This model-based elasticity equation provides the basis for quantitative elasticity reconstruction method.

In acousto-mechanical imaging, the goal of elasticity reconstruction is to estimate an unknown distribution of Young's modulus based on the simultaneous and synchronized measurement of normal stress at the surface $S_{\sigma u}$ and internal displacement within the ultrasound imaging plane S_l (see Fig. 1). As illustrated in Fig. 2, the iterative elasticity reconstruction starts with initial guess of Young's modulus distribution. The displacement and strain fields are then computed using solution of the model-based elasticity equation presented above, and stress pattern at the surface is estimated. With every iteration, the elasticity distribution is adjusted to minimize the global error δ:

$$\delta = \int_{S_l} (u_l - u_l^*)^2\,ds +$$

$$\int_{S_u} \sum_{i=1}^{3} (u_i - u_i^*)^2\,ds + \int_{S_{\sigma u}} \sum_{i=1}^{3} \left[(u_i - u_i^*)^2 + \Big(\sum_{j=1}^{3} (\sigma_{ij} - \sigma_{ij}^*) n_j\Big)^2 \right] ds + \int_{S_\sigma} \sum_{i=1}^{3} \Big(\sum_{j=1}^{3} (\sigma_{ij} - \sigma_{ij}^*) n_j\Big)^2\,ds \ ,$$

where the measured or otherwise known parameters are denoted with asterisk, u_l and u_l^* are model-predicted and ultrasonically measured axial displacement in the imaging plane, and nj is the jth component of the unit normal vector at the surface $S_{\sigma u}$, S_σ and S_u are the surface of the tactile sensor, the remaining top surface, and the bottom surface of the breast, respectively (the geometry is schematically presented in Fig. 1). In most cases of breast tactile imaging, the σ_{ij}^* at the S_σ surface will be set to zero. Similarly, the displacements u_i^* at the bottom surface S_u are also zero. By itself, the measured internal displacement provides additional stability of the error minimization procedure. Moreover, compared to mechanical imaging system, the ultrasound B-Scan can provide the overall geometry of the breast and possibly the geometry and location of the lesion – this information can be used both to refine initial Young's modulus guess and to enhance the elasticity minimization procedure.

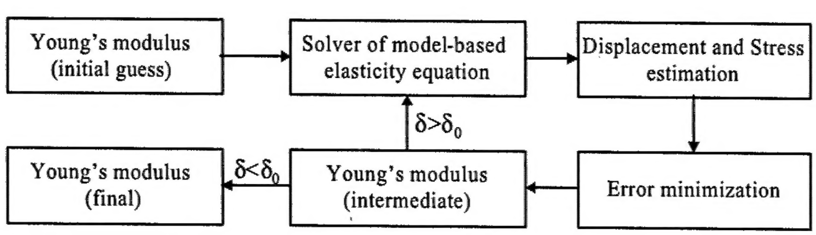
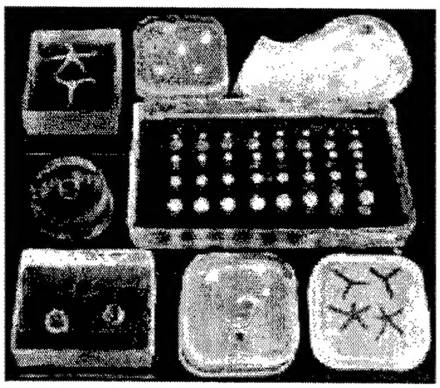


Figure 1: Block-diagram of elasticity reconstruction procedure implemented in acousto-mechanical imaging. Both displacement and stress measurements are used simultaneously to estimate Young's modulus distribution within the imaging plane.

Once the minimization condition $\delta<\delta_0$ is reached, the resulting elasticity distribution is outputted to outline both absolute Young's modulus values and geometry of the identified lesion. Then, the elasticity image within ultrasound imaging plane can be further refined. From the initial 3-D Young's modulus map, an approximate plane of symmetry containing the lesion can be identified, and acousto-mechanical deformation experiment is performed in this plane. As described previously [Skovoroda et al 1994 and 1995], accurate and direct (i.e., without any assumptions) absolute 3-D elasticity reconstruction can be performed in this plane combining internal strain and surface stress measurements.

Phantom fabrication:

Based on the literature data, the material for adequate manufacturing of mechanical models of breast should cover the range of Young's modulus from 5 to 500 kPa. In addition, a compatible material with Young's modulus on the order of 1MPa is needed to simulate the skin covering the breast internal tissues. We have tested various polymer materials and developed techniques to reliably produce tissue-mimicking phantoms of a wide variety of sizes and internal complexities within these modulus ranges (Figure 3). Within the scope of this project, we constructed several phantoms to test the ability of the AMI to detect internal elasticity variations.



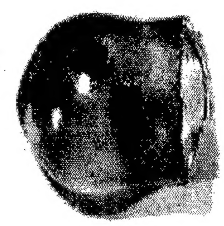


Figure 3: Breast and tissue mimicking polymer phantom.

We will then construct a final set of phantoms closely mimicking both size and shape of the breast to perform careful evaluation of the developed acousto-mechanical imaging.

Prototype of the AMI imaging system:

The initial prototype of acousto-mechanical imaging system is illustrated in Fig. 4, where the ultrasound imaging transducer is enclosed into assembly containing 4 rows of 16 pressure sensors – 2 rows on each side of the transducer – extending the entire lateral dimension of the ultrasound imaging array. The signals from the entire array of pressure sensors can be acquired at 108 frames per second simultaneously with real-time ultrasound frames. The mechanical imaging system is interfaced with a computer that is capable of displaying surface stress maps in real-time. To demonstrate how the acousto-mechanical imaging system can detect and quantify absolute elasticity distribution, the experiment was performed on polymer-based phantom containing a single hard circular inclusion. During the deformation of the phantom, frames of both ultrasound data and surface stress were collected.

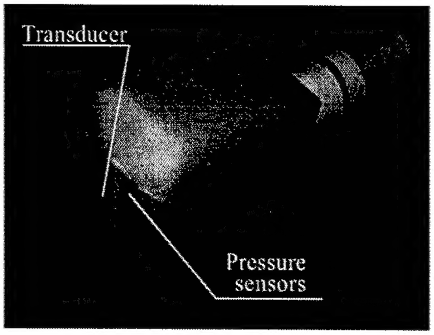


Figure 4: Photograph of the ultrasound transducer interfaced with the pressure-sensing array.

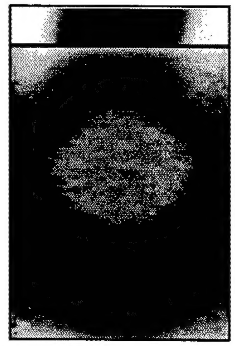


Figure 5: Surface stress (top) and internal displacement (bottom) maps simultaneously acquired during acousto-mechanical imaging study of the phantom with a single hard inclusion.

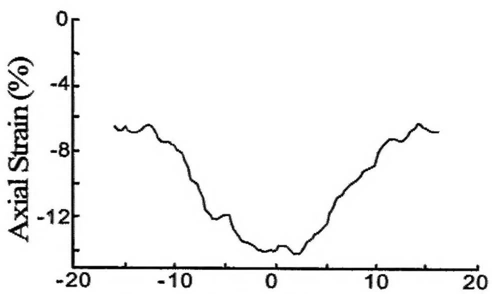


Figure 6: Magnitude of axial strain at the surface of the phantom.

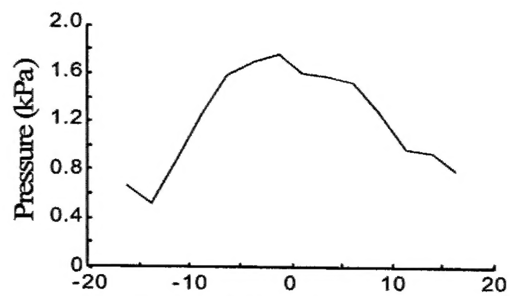


Figure 7: Axial stress distribution at the surface of the phantom.

In Fig. 5, the surface stress over the footprint of the transducer (top) and the distribution of axial strain within the 32-mm by 50-mm region of the phantom (bottom) are shown. For this experiment, the magnitude of the axial strain near the top surface (Fig. 6) should be proportional to the stress (or pressure) at the surface (Fig. 7) since the material at the top of the phantom is homogeneous – this can be clearly seen in the profiles presented. By measuring the necessary components of internal displacements and strains, the direct (i.e., without any assumptions) but relative elasticity reconstruction can be performed. Then the overall elasticity distribution can be adjusted to match the surface stress as measured by the mechanical imaging system resulting in imaging of absolute tissue elasticity. In addition to the absolute reconstructive elasticity imaging, the acousto-mechanical imaging system can assist in freehand and strain-hardening imaging.

KEY RESEARCH ACCOMPLISHMENTS:

- Design, development and fabrication of pressure sensor array for acousto-mechanical imaging (in cooperation with Pressure Profile Systems, Inc. and Artann Laboratories, Inc.)
- Development of stress data acquisition circuitry including digital interface for PC-based data capture (in collaboration with Artann Laboratories, Inc.)

- Development of data acquisition software including user friendly graphical interface (in collaboration with Artann Laboratories, Inc.)
- Design and fabrication of breast mimicking tissue models(in collaboration with Artann Laboratories, Inc.)
- Development of model-based elasticity reconstruction algorithm
- Integration and synchronization of all components of the acousto-mechanical imaging system(in collaboration with Artann Laboratories, Inc.)
- Design and development of a prototype of the acousto-mechanical imaging system (in collaboration with Artann Laboratories, Inc.)
- Initial test of the acousto-mechanical imaging system

REPORTABLE OUTCOMES:

Skovoroda AR, Aglyamov SR, Sarvazyan AP, O'Donnell M, and Emelianov SY, "Acousto-mechanical imaging: assessment and validation using analytical and numerical modeling," IEEE Transactions on Medical Imaging, 2002 (in preparation).

"3D stress/strain imaging and biopsy guidance application" – SBIR phase I and II grant proposal, PI: Dr. J. Son (submitted to NIH, July 2002)

Note: As described in the main body of this report, there were some unforeseen delays in finding the preferred manufacturer of the pressure sensor array compatible with ultrasound imaging system. The development of Acousto-Mechanical Imaging, therefore, was delayed by approximately 6 months. Consequently, not all of the reportable outcomes are yet available while we are actively pursuing the final stages of the project.

CONCLUSIONS:

Acousto-mechanical imaging digitally captures the human sense of touch to provide maps of the underlying tissue structure in terms of its mechanical properties. As described above, this modality may have far greater sensitivity than manual palpation over a representative range of lesion sizes and depths. Moreover, it can detect the impalpable lesions thus extending the limited range of manual breast examination. Therefore, the acousto-mechanical imaging holds great promise for improving early detection and diagnosis of breast cancers. This promise is greatly amplified by relatively simple and inexpensive implementation of the acousto-mechanical imaging – an adjunct to the existing imaging studies of the breast. In addition, 3-D visualization is possible in acousto-mechanical imaging – this can find a broad range of clinical applications ranging from improved breast biopsy procedures to quantitative evaluation of breast masses and composition. Finally, because of the correlation between the mechanical and histopathological properties of lesions, the acousto-mechanical imaging can provide a mean for non-invasive detection and differentiation of breast pathology.

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APPENDICES:

None